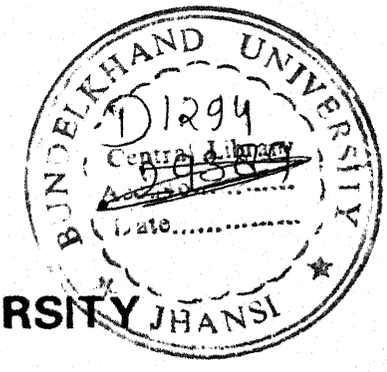
PROSPECTIVE STUDY OF EFFECT OF CONVERT ENZYME INHIBITORS, CAPTOPRIL VS LISINOI ON PROTEINURIA AND RENAL FUNCTION IN DIABETIC NEPHROPATHY

THESIS

For

DOCTOR OF MEDICINE

(MEDICINE)



BUNDELKHAND UNIVERSITY
JHANSI (U. P.)

1994 **SOBARAN SINGH P**

D E D I C A T E D

T O

L O V I N G M E M O R Y

O F

M Y P A R E N T S

C E R T I F I C A T E

This is to certify that the work entitled "PROSPECTIVE STUDY OF EFFECT OF CONVERTING ENZYME INHIBITORS, CAPTOPRIL Vs LISINOPRIL ON PROTEINURIA AND RENAL FUNCTION IN DIABETIC NEPHROPATHY", which is being submitted as a thesis for M.D.(Medicine) Examination, 1994 of Bundelkhand University, has been carried out by Dr. Sobaran Singh Pal in the department of Medicine, M.L.B. Medical College, Jhansi.

He has put in the necessary stay in the department as per university regulations.

Dated: 27th Sept., 1993

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M.D., D.Sc.,
Professor and Head,
Department of Medicine,
M.L.B. Medical College,
JHANSI.

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Dated : 27th Sept., 1993

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MD, MNAMS,
Assistant Professor,
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M.L.B. Medical College,
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(GUIDE)

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A C K N O W L E D G E M E N T

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Lastly I give my thanks to all those unnamed persons who were associated with this work.

Dated : 27th Sept., 1993.

(Sobaran Singh Pal)

C O N T E N T S

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I N T R O D U C T I O N

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INTRODUCTION

Diabetes mellitus is a common serious metabolic disorder. Its true frequency varies from 1-2% in general population. Disease is characterised by metabolic abnormalities in the form of hyperglycemia, hyperlipidemia and glycosuria.

Common complications are retinopathy, diabetic nephropathy, ischemic heart disease and atherosclerosis.

Renal disease is the commonest complication and leading cause of death in diabetes. Diabetes affects the structure and function of kidney in many ways. Diabetic nephropathy is presented with variety of clinical syndromes like mild asymptomatic proteinuria, nephrotic syndrome, hypertension and progressive renal failure.

Diabetic nephropathy represents the single most important cause of renal failure in adults in the western world, causing 25% of all new cases of uremia. The peak incidence for the development of clinical renal disease occurs after about 16 years of insulin dependent diabetes mellitus. Over all, approximately 35-45% of patients, with long standing insulin dependent diabetes mellitus will ultimately develop diabetic nephropathy, defined as dipstick positive proteinuria, hypertension and falling GFR (Christiansen and Anderson et al, 1985).

In insulin dependent diabetic patients incidence of nephropathy is 40-50% (Wetzel et al, 1986) while less

in non insulin dependent diabetes. One in four end stage renal disease patients turns out to be diabetic(Mogensen, 1984). The mortality in patients suffering from diabetic nephropathy is upto 100 times that of age and sex matched background population, and this is mainly due to enormous deaths from end stage renal disease (Borch Johnsen et al, 1985).

During the first decade of diabetes, values for urinary albumin excretion rate usually remains normal, averaging $<$10 mg/day there are, however, at least two circumstances in which transient increase in urinary albumin excretion may be observed in patients with early diabetes. First, elevation of UAE may be observed during episodes of poor metabolic control. Values for UAE in this setting usually remains $<$50 mg/day but higher values have some times been recorded.

Second, exercise may increase UAE to values as high as 500 mg/day in diabetic patients whose reading values for UAE are normal (Vittinghus and Mogensen, 1982).

Diabetic nephropathy is diagnosed by urinary excretion of protein in the range of 30-300 mg/24 hours which is called as microalbuminuria and more than 300 mg/24 hours is clinical proteinuria (Mogensen et al, 1987). In microalbuminuria cases, renal functions are normal and urine is negative for clinical proteinuria (Vibreti et al, 1979).

Diabetic nephropathy progression leads to glomerulosclerosis which causes decreased nephron population along with increase in single nephron GFR and leads to solute over load of that single nephron causing damage to endothelium, mesothelium, epithelium, ultimately frank proteinuria and renal failure.

Diabetic nephropathy is classified in 5 stages of Mogensen et al (1976).

Stage I : Early renal hypertrophy and hyperfunction.

Stage II : Renal lesion without clinical signs.

Stage III : Incipient diabetic nephropathy.

Stage IV : Clinical overt.

Stage V : End stage renal failure.

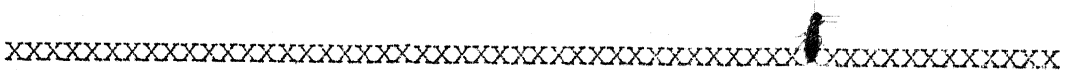
The observations that proteinuria precedes loss of renal function in diabetic patients has led naturally to the assumption that maneuvers which reduce proteinuria will also retard the progression of diabetic renal disease. Morphometric studies suggest that the reduction of GFR in diabetic nephrology is caused by progressive expansion of the glomerular mesangium. It is not certain that all maneuvers which reduce proteinuria will prevent reduction of the GFR in diabetic patient.

Microalbuminuria is now considered to be a marker of earlier renal disease in IDDM patients and an indicator of susceptibility to cardiovascular complications.

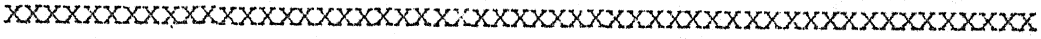
Several therapeutic interventions, such as glycemic control, antihypertensive treatment and low to moderate protein diets have been shown to be effective in reducing microalbuminuria (Brouhard and Lagrone, 1990; Ciavarella et al, 1987; Evanoff et al, 1987; Kupin et al, 1987; Rudberg et al, 1988 and Zeller et al, 1991).

The management of diabetic patients with advanced nephropathy is not easy, because such patients tends to have the nephrotic syndrome and severe damage of many other organs, consequently, it would be of great value to try and alleviate the massive proteinuria which is characteristic of this condition. In early stages of diabetic nephropathy, several maneuvers and drugs have been tried to reduce the proteinuria and retardation of progression of nephropathy. Now-a-days ACE inhibitors are much in use specially captopril for the reduction of proteinuria and improvement of renal function in diabetic nephropathy cases.

Recently lisinopril which is being argued as a better ACE inhibitor as compared to captopril in the management of hypertension, has been utilized in diabetic nephropathy cases. One to the paucity of literature about the use of lisinopril in diabetic nephropathy with or without hypertension, thus study has been designed to know the effect of captopril versus lisinopril in cases of diabetic nephropathy.



REVIEW OF LITERATURE



REVIEW OF LITERATURE

About 35 percent of patients with insulin dependent diabetes develop persistent proteinuria, a decline in glomerular filtration rate and increased arterial blood pressure, which collectively constitute the clinical syndrome of diabetic nephropathy. The major pathologic changes of diabetes include thickening of all renal extracellular basement membranes and mesangial matrix, and mesangial cell expansion. Although much less is known regarding renal pathology in NIDDM compared to IDDM, most proteinuric patients with NIDDM have typical diabetic nephropathy while approximately 25 percent have another form of renal disease. It is commonly thought that nephropathy is more common in IDDM patients (Herman and Teutsch, 1985). Recent studies of diabetic Pima Indian suggest that the cummulative risk of nephropathy in these NIDDM patients is at least as high as in IDDM patients. The high mortality is due to an excess of cardiovascular mortality and to end stage renal disease.

Several studies dealing with small number of patients have shown that effective antihypertensive treatment postpones renal insufficiency in insulin dependent diabetics with nephropathy.

ACE INHIBITORS

Renin is an enzyme produced by kidney in response to adrenergic activity and to sodium depletion. Renin converts a circulating globulin (angiotensinogen) into the biologically inert angiotensin-I, which is then changed by angiotensin converting enzyme(ACE) into the highly potent vasoconstrictor angiotensin-II. Angiotensin II also stimulates production of aldosterone (sodium retaining hormone by the adrenal cortex). It is evident that angiotensin-II can have an important effect on blood pressure.

CAPTOPRIL

This synthetic compound, D-3-mercapto-2-methyl Propanoyl-L-Proline, competitively inhibits the angiotensin converting enzyme, depeptidyl carboxypeptidase, and thus blocks the generation of angiotensin-II. As ACE is also important for the inactivation of the potent vasodepressor bradykinin, its blockade raises the plasma bradykinin level which contribute to the fall in blood pressure. It causes renal vasodilatation and increased G-F-R and reduction in after load.

Drug is given orally in empty stomach and therapy is usually initiated with 12.5 mg to 25 mg three times a day and maximum dose 50 mg three times a day. Smaller doses are used in renal insufficiency captopril has half life of 2 hours and is partly metabolised and partly excreted unchanged.

Adverse effects of captopril are pruritis, skin rashes loss of taste, sensation, stomatosis, abdominal pain, liver damage, raised plasma potassium, proteinuria and impairment of renal function with high doses are very serious adverse effects.

LISINOPRIL

Lisinopril is a lysine derivative of enalaprilate the active antiotensin-converting enzyme inhibitor metabolite of enalapril. Lisinopril decreases plasma concentration of angiotensin-II and aldosterone.

About 25-50 percent of an oral dose of lisincpril becomes bioavailable in man and peak serum concentration of lisinopril are reached in about 6 hours. Absorption is unaffected by food. Lisinopril is active by itself and does not require to undergo activation in the liver. Absorbed drug is primarily excreted unchanged in urine.

The most frequently reported side effects during clinical trials with lisinopril included dizziness, headache, cough, hypotension and diarrhoea.

The initial dosage in patients with normal renal function is 5-10 mg once daily in hypertension. Doses can be increased according to patient response, upto a maximum of 40 mg once daily in patients with hypertension.

Viberti and Hill et al (1982) studied that the over night urinary albumin excretion rate(AER) in 87

patients with insulin dependent diabetes mellitus was measured in 1966-67. Fourteen years later information was obtained on 63 of the original cohort, those alive were restudied and for those who had died relevant clinical information and cause of death were recorded. The development of clinical diabetic nephropathy (Albustix-positive proteinuria) was related to the 1966-67 AER values. Clinical proteinuria developed in only 2 of 55 patients with AER below 30 ug/min but in 7 of 8 with AER between 30 and 140 ug/min. The risk of clinical diabetic nephropathy in the later group was twenty four times higher than in the former. 9.1% of patients with AER below 30 ug/min had died, compared with 37.5% with higher AER. The two groups did not differ significantly in age, sex composition and initial blood pressure, thus elevated levels of microalbuminuria strongly predict the development of clinical diabetic nephropathy. These levels of AER are potentially reversible and their detection and treatment may prevent diabetic renal disease.

Among therapies examined to date, antihypertensive agents have proven most effective in reducing proteinuria in patients with diabetic renal disease. Moreover, antihypertensive agents have the same effect on glomerular barrier function over all studies to date suggested that albumin excretion rates are comparably reduced the regimens including converting enzyme inhibitors and beta adrenergic receptor blockers, while

variable effects on albumin excretion rates have been observed with calcium channel antagonists.

The mechanism by which antihypertensive agents improve glomerular barrier function in diabetic renal disease have not been fully elucidated. It has frequently been suggested that antihypertensive agent improve glomerular barrier function by lowering glomerular transcapillary hydraulic pressure. A recent modification of this "hemodynamic" hypothesis suggested that antihypertensive agents improve glomerular barrier function by reducing glomerular capillary wall tension, which is considered to be the product of $\triangle$ P and glomerular capillary radius studies in which converting enzyme inhibitor treatment was initiated at the outset of experimental diabetes are often cited in support of this hypothesis.

These studies have shown that continuous converting enzyme inhibitor treatment reduces $\triangle$ P and largely prevents development of albuminuria in rats, there is reason to question, however, whether lowering of capillary wall tension accounts for the beneficial effect of antihypertensive agents on glomerular barrier function in established diabetic nephropathy.

A recent dextran clearance study suggested, alternatively, that converting enzyme inhibitor therapy may have a direct effect on glomerular capillary wall pore structure. Regarding this study, 16 diabetic patients

with serum creatinine values $\angle$0.2 mg/dl and proteinuria averaging 2.2 g/day were treated with a converting enzyme inhibitor for 90 days. Values for GFR remained stable during converting enzyme inhibitor treatment while mean arterial pressure declined from 98$\pm$3 to 92$\pm$3 mm Hg. Converting enzyme inhibitor treatment decreases fractional clearance values not only for large dextran molecules with radii of 50-60° A°, but also for dextran molecules with radii of 30-50 A°. This finding indicates that converting enzyme inhibitor therapy alters the structure of the capillary wall so as to shift the entire pore-sized distribution towards a lower values.

Nyberg et al suggested that hyperglycemia is a risk factor for the progression of clinical diabetic nephropathy in insulin dependent diabetic patients with impaired renal function (glomerular filtration rate $\angle$ 50 ml/min.).

Mogensen et al (1982) studied that during antihypertensive treatment the mean systolic blood pressure fell to 144 mm Hg and mean diastolic pressure to 95 mm Hg. In the control period five patients had shown a mean monthly decline in glomerular filtration rate of 1.23 ml/min with antihypertensive treatment, however, this fell to 0.49 ml/min (2P = 0.042). In the remaining patients the glomerular filtration rate was 137 ml/min. before treatment and 135 ml/min at the end of treatment

period. In all patients the mean yearly increase in albumin clearance fell from 107% before treatment to 5% during treatment (2P = 0.0099). This small study indicated that antihypertensive treatment slows the decline in renal function in diabetic nephropathy.

Poring et al (1983) showed that blood pressure is very important for renal functions in diabetic nephropathy. Treatment of hypertension has been repeatedly documented as beneficial in reducing the rate of deterioration of renal functions when nephropathy is present.

Yoshio Taguma et al (1985) investigated whether captopril, an angiotensin converting enzyme inhibitor, would reduce proteinuria in patients with advanced diabetic nephropathy. Captopril (37.5 mg given in divided doses three times daily) was administered to 10 azotemic diabetics with heavy proteinuria. Urinary protein decreased promptly within two weeks (from 10.6$\pm$ 2.2 to 6.1$\pm$1.4 gm/day, p $<$0.01). The decrease in proteinuria did not coincide with a fall in systemic blood pressure. Serum creatinine values did not change in any of the patients except one.

The study suggested that captopril caused a decrease in intrarenal hypertension, which contributed to the reduction of urinary protein excretion.

Bjorck Staffan et al (1986) studied 15 patients with insulin dependent diabetes mellitus. All had

diabetic nephropathy, the diagnosis being based on the presence of retinopathy, a suitable time relation between the onset of diabetes and proteinuria and a decline in kidney function. The mean age of patients was 34 years, and mean duration of diabetes was 22 years. All patients had hypertension, and in 14 patients blood pressure was 95 mm Hg or higher when they were included in the study.

Thirteen patients were given captopril and frusemide in combination and in one case metaprolol was also used during two years treatment with captopril in 14 patients the mean arterial blood pressure had fallen by 5 mm Hg ($p < 0.05$) and deterioration in glomerular filtration rate had decreased from 10.3 to 2.4 ml/min/year ($p < 0.05$).

The mean serum creatinine concentration was 2.1 mg/100 ml before treatment with captopril and 2.5 mg/100 ml at the end of the follow up period.

The mean$\pm$SD urinary protein excretion was 2.9 (2.0) gm/24 hour before and 2.8(1.9) gm/24 hour after treatment with captopril. Protein excretion was reduced in 10 of the 14 patients, but not significantly. Prctein excretion was not significantly correlated with the rate of deterioration in glomerular filtration rate or mean arterial pressure.

Hommel, (1986) studied the effect of 12 weeks, monotherapy with captopril (25-50 mg twice a day) in 10

hypertensive IDDM patients with persistent albuminuria. In an initial one week randomised single blind trial of captopril versus placebo, captopril (for nine patients) reduced arterial blood pressure from 148/94 (SD 11/6) to 135/88 (8/7) mm Hg ($p < 0.05$), and albuminuria from 1549 (range 352-2238) to 1170 (297-2198) ug/min ($p < 0.05$), while glomerular filtration rate remained stable. No significant changes occurred in seven patients treated with placebo.

During the 12 weeks of captopril treatment aterial blood pressure in all patients fell from 147/94 (11/6) to 135/86 (13/7) mm Hg ($p < 0.01$), albuminuria fell from 1589 (range 168-2588) to 1075(35-2647) ug/min/1.73 m^2 ($p < 0.01$). The renin angiotensin system showed suppressed plasma concentration of angiotensin II and increased plasma concentration of angiotensin I and renin.

The study showed that glomerular filtration rate is not dependent on angiotensin-II, that captopril reduces albuminuria, probably by lowering glomerular hypertension and that captopril represents a valuable new drug for treating hypertension in diabetics dependent on insulin with nephropathy.

Parving et al (1987) suggested that raised arterial blood pressure is often found early in diabetic nephropathy. A progressive rise in blood pressure occurs with declining kidney function. The interval between

onset of persistent proteinuria and rising of serum creatinine concentration above the normal limits is considerably shorter in hypertensive compared with normotensive insulin dependent diabetics with nephropathy.

Systemic and glomerular hypertension enhances the development of diabetic nephropathy. Conversely, effective antihypertensive treatment reduces albuminuria and diminishes the rate of decline in glomerular filtration rate.

Parving (1988) studied to assess whether long term inhibition of angiotensin converting enzyme with captopril and frusemide or bendroflurazine protects the kidney function.

Treatment group of 18 hypertensive insulin dependent diabetics with nephropathy were given daily captopril 37.5-100 mg and frusemide (mean 98 mg (10 patients) or bendroflurazide (mean) 4 mg (7 patients). The treatment was continued for about two and a half years. Controls were not treated.

Baseline values were identical in treated and untreated groups respectively. Mean blood pressure 146/93 (SE 3/1) mm Hg Versus 137/95 (2/1) mm Hg and geometric mean albuminuria 982 (antilog SE 1.2) ug/min Versus 936(1.2) mg/min and mean glomerular filtration rate 98(SE 5)/ml/min/1.73 M^2 Versus 96(6) ml/min/1.73 M^2. Mean arterial blood pressure fell by 8.7 (1.3) mm Hg with captopril and raised by 6.6 (0.5) mm Hg in controls

($p < 0.001$). Albumin excretion decreased to 390(1.1) ug/min with captopril and raised to 1367(1.3) ug/min in controls ($p < 0.001$). The rate of decrease in glomerular filtration rate was lower with captopril 5.8(0.7) ml/year Versus 10.0(1.3) ml/year) ($p < 0.01$).

Captopril is a valuable new drug for treating hypertension in insulin dependent diabetics with nephropathy.

Sipahe Lee et al (1990) have investigated whether long term administration of captopril would reduce proteinuria and preserved renal function more effectively than other antihypertensive in patients with diabetic nephropathy and hypertension.

Twenty two patients were divided into two groups. Group I (11patients) treated with antihypertensive medication including captopril and another group II (11 patients) were treated without captopril and they were followed up for average 20 months (6-32 months).

Regarding proteinuria, in group I, 24 hours urine protein decreased promptly from 7.4 ± 3.4 gm (n=11) to 4.1 ± 2.6 gm (n=8) in 2 weeks ($p < 0.005$) and there after continuously reduced to 3.6 ± 0.6 gm (n=5) in 24 months ($p < 0.05$), but in group II proteinuria increased progressively from 2.9 ± 2.3 gm (n=11) to 5.8 ± 4.8 gm (n=4) in 24 months.

Serum creatinine increased from 1.72 ± 0.43 mg/dl (n=11) to 3.45 ± 0.67 mg/dl (n=5) ($p < 0.01$) in 24 months

in group I, whereas from 1.32±0.23 mg/dl (n=11) to 4.15 ±3.01 mg/dl (n=6) in group II.

In conclusion, long term captopril treatment in patients with diabetic nephropathy and hypertension can be effective in preserving renal function and delaying progression of chronic renal failure, in addition to reduction of proteinuria.

Kibriya and Khan et al (1990) assessed the effect of captopril and nefedipine on kidney function in 20 patients with NIDDM with persistent proteinuria. Patients were divided into two equal matched groups. Group I received captopril and group II received nefedipine. After 8 weeks of captopril therapy, the mean arterial blood pressure reduced from 144/85 to 136/82 mm Hg and proteinuria from 6000(684) to 1962(400) ug/min ($p < 0.001$) while blood urea from 8.7 to 7.5 m mol/l and creatinine (166.0 to 166.0 m mol/l) remained stable.

Patients receiving nefedipine, their mean arterial blood pressure reduced from 144/84 to 135/82 and proteinuria from 4127(424) to 1740(387) ug/min (p = not significant) while blood urea (8.9 to 9.1 m mol/l) and creatinine (151 to 154 m mol/l) remained same after the similar period of study, when two groups were compared together, there is significant percent reduction of proteinuria in captopril group (64%) as compared to nefedipine group (8%).

Captopril reduces proteinuria in patients with diabetic nephropathy of NIDDM origin.

Though much literature is not available on the study of effect of lisinopril on diabetic nephropathy, but its effect has been seen on renal function. In a 12 weeks study on elderly patients with hypertension, Mark S. Laher et al (1990) saw its long term effects on renal and metabolic functions. They observed that there was no change in GFR after 12 weeks of therapy which remained unaltered even after 1 year of treatment. Besides, the renal blood flow was significantly increased at the end of first year after treatment.

Many studies have shown lisinopril to be effective in the treatment of all grades of hypertension both as monotherapy and in combination with a thiazide diuretic (Bolzano et al, 1987; Donohoe et al, 1988; Mortin et al, 1987; Pool et al, 1987, Zachariah et al, 1987).

The stability of GFR was consistent with observations made in studies with lisinopril in patients with essential hypertension or with impaired renal function (Dupont et al, 1987; Donohoe et al, 1988 and Gabriel et al, 1987).

AIMS AND OBJECTIVES OF THE STUDY

This study has been designed to find out the effect of captopril versus lisinopril in diabetic nephropathy with or without hypertension on :

a. Proteinuria and

b. Renal function.

M A T E R I A L   A N D   M E T H O D S

MATERIAL AND METHODS

The study has been conducted on the patients of diabetic nephropathy, attending the diabetic and nephrology clinics of out patient department and admitted in M.L.B. Medical College, Hospital, Jhansi.

The history was taken from all the patients of diabetes to know the duration of symptoms, year of diagnosis, type of diabetes, familial relation and complication of disease.

General as well as systemic examinations were recorded to know the general condition, pulse, blood pressure, temperature, pallor, icterus, cyanosis, clubbing, oedema, hydration and lymphadenopathy. Systemic examination was done to find out the changes in all systems due to diabetes. The patients having disease other than diabetes were excluded from the study.

Dipstick test and fundoscopy were done to find out the proteinuria and retinopathy. After confirmation of the diabetic nephropathy, the patients were investigated for 24 hours proteinuria, blood urea, serum creatinine and glomerular filtration rate.

The blood pressure was recorded before starting drugs. The captopril and lisinopril were given to the alternate patient respectively. The doses of drugs were adjusted according to the blood pressure response. Hypoglycemic drugs were given according to blood sugar levels.

After 8 weeks course of converting enzyme inhibitors, patients were further investigated for 24 hour urine protein excretion, blood urea, serum creatinine and GFR. At last, the results were compiled to know the efficacy of drugs in relation to reduction in proteinuria and improvement in renal functions of individual drugs as well as statistical analysis was done to find out the difference in efficacy.

URINE PROTEIN

A quantitative estimation of protein was done by turbidity method as described by Wooton (1964).

Reagent

Sulphosalicylic acid (3%) : 3.0 gm of sulphosalicylic acid was dissolved in 100 ml distilled water.

Protein standard solution (100%) : In 100 ml distilled water, 100 mg crystalline bovine albumin was dissolved and kept in refrigerator.

Procedure

Twenty four hours urine was collected in bottle which was marked in milli litres so the 24 hours urinary volume was measured and noted. Toluene was used as preservative. Required amount was then taken from it and centrifuged.

Test

1.	Urine	1.0 ml
2.	Sulphosalicylic acid solution	4.0 ml

Standard

1.	Protein standard solution	1.0 ml
2.	Sulphosalicylic acid solution	4.0 ml

Blank

1.	Urine	1.0 ml
2.	Water	4.0 ml

The tubes were kept for 30 minutes and then the absorbance was measured with blue filter (450 nm) against reagent blank.

Calculation

$$\text{Urinary protein (mg/l)} = \frac{\text{Reading of test}}{\text{Reading of standard}} \times 1000$$

BLOOD UREA (Diacetyl Monoxime Method)

Reagents

1. Diacetyl mono-oxime reagent : 2 gm pure diacetyl mono-oxime was dissolved in 60 ml double distilled water and 2 ml glacial acetic acid was mixed and made it 100 ml with double distilled water.

2. Acid mixture : 150 ml of 85% phosphoric acid was added to 140 ml of double distilled water. Mixed well 50 ml of concentrated sulphuric acid was added slowly.

3. Trichloroacetic acid solution : 10 gm TCA dissolved in 100 ml double distilled water.

4. Urea stock standard : 250 mg of pure urea crystals dissolved in 100 ml double distilled water.

5. Working urea standard : 1 ml of stock solution was diluted in 100 ml of double distilled water. This solution contains 0.25 mg/urea/ml.

METHOD

0.1 ml blood sample was added in a tube containing 1.9 ml double distilled water. It was mixed thoroughly and 2.0 ml 10% TCA solution was added and centrifuged the content at 3000 rpm for 5 to 10 minutes. 2 ml supernatant was taken in a test tube and it was marked as 'T' representing the test blood sample filtrate.

Standard

1.0 ml of working urea solution was added in 1.0 ml of double distilled water. It was marked as 'S' representing standard solution.

Blank

2.0 ml double distilled water was taken and it was marked as 'B' representing the blank system.

There after 0.4 ml diacetyl mono-oxime reagent and 1.6 ml acid mixture were added in each system. Mixed well and incubate for 30 minutes in boiling water bath. After that test tubes were taken out and measured the samples at 480 nm by setting the spectrophotometer zero with the blank system.

Calculation :

$$\text{Blood urea (mg/dl)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 100$$

SERUM CREATININE (Alkaline picrate method)

Reagents

1. Sodium hydroxide 0.75 N solution : It was prepared by dissolving 30 gm of sodium hydroxide in 1 litre of double distilled water.
2. Picric Acid Solution : Picric acid solution was prepared in double distilled water. This solution is called to be saturated when some crystals of picric acid settled down at the bottom and did not dissolve even after thorough mixing.
3. Sodium Tungstate (57 W/V) : It was prepared by dissolving 5.0 gm pure sodium tungstate in 100 ml double distilled water.
4. Sulphuric acid (2/3 N) : It was prepared by mixing 10 ml concentrated sulphuric acid to the 900 ml double distilled water and made upto the 1 litre with water.
5. Stock Creatinine standard : 20 mg pure creatinine was dissolved in 100 ml double distilled water. It was 20 mg% creatinine solution.
6. Working creatinine standard : 1.0 ml of creatinine stock solution was diluted with 10 ml double distilled water. It was 2 mg% creatinine solution.

METHOD

Sets of 3 test tubes were taken and marked as 'T' for test, 'S' for standard and B for blank. Solutions were taken as follows :

In 'T' test tube : 1.0 ml of serum and 1.0 ml double distilled water.

In 'S' test tube : 2 ml working creatinine standard solution.

In 'B' test tube : 2.0 ml double distilled water.

After that 1 ml 5% sodium tungstate solution and 1 ml 2/3 N sulphuric acid were mixed and centrifuged for 5 to 10 minutes at 3000 rpm.

In another set of the test tubes marked with 'T' 'S' and 'B', the 2 ml supernatant was taken from the above respective systems. Now 0.5 ml picric acid solution and 0.5 ml 0.75 N sodium hydroxide solution were used respectively in each system. It was incubated at room temperature for 20 minutes and readings were taken from the test and standard samples at 520 nm by setting the spectrophotometer at zero with the blank.

Calculation

$$\text{Serum creatinine (mg/dl)} = \frac{\text{Reading of unknown}}{\text{Reading of standard}} \times 4$$

GLOMERULAR FILTRATION RATE (GFR)

It was calculated with the help of following formula :

$$\text{Cl Cr (ml/min)} = \frac{(140-\text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85 \text{ for women}$$

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O B S E R V A T I O N S

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A total of 33 patients were included in this present study, who were attending diabetic clinic regularly in M.L.B. Medical College, Hospital, Jhansi (U.P.). Out of 33 patients, 16 patients were put in captopril group while remaining 17 patients in lisinopril group. Blood pressure as well as glycemic control was satisfactory in follow up periods.

TABLE I : Distribution of cases of captopril group according to their age and sex.

Age groups (years)	Male		Female		TOTAL	
	No.	%	No.	%	No.	%
21 - 30	1	9.1	2	40.0	3	18.75
31 - 40	2	18.2	-	-	2	12.50
41 - 50	3	27.3	3	60.0	6	37.50
51 - 60	4	36.4	-	-	4	25.00
61 - 70	1	9.1	-	-	1	6.25
TOTAL	11	100.0	5	100.0	16	100.00

Table I shows that there were 16 patients in this group. Out of which 11 were males and 5 females. The maximum number (37.5%) of cases belonged to 41-50 years of age group. Male patients were maximum in age group of 51-60 years (36.4%) whereas female patients were maximum in the age group of 41-50 years (60%).

TABLE II : Distribution of cases of lisinopril group according to their age and sex.

Age group (years)	Male		Female		Total	
	No.	%	No.	%	No.	%
21 - 30	1	10.0	-	-	1	5.8
31 - 40	1	10.0	2	28.6	3	17.6
41 - 50	4	40.0	-	-	4	23.5
51 - 60	1	10.0	4	57.1	5	29.5
61 - 70	3	30.0	1	14.3	4	23.5
TOTAL	10	100.0	7	100.0	17	100.0

Table II shows age and sex distribution of cases of lisinopril group. There were 17 patients in this group. Out of which 10 were males and 7 females. The maximum (29.5%) cases belonged to 51-60 years of age group. Male patients were maximum in age group of 41-50 years (40%) whereas females were maximum (57.1%) in the age group of 51-60 years.

TABLE III : Distribution of cases of captopril group according to duration of diabetes mellitus.

Duration of D.M. (years)	No.of cases	Percentage
1 - 5	9	56.3
6 - 10	6	37.5
11 - 15	1	6.3
TOTAL	16	100.0

Table III shows distribution of cases of captopril group according to their duration of diabetes mellitus. The maximum number of cases (56.3%) belonged to 1-5 years of duration of diabetes mellitus whereas minimum (6.3%) cases in the range of 11-15 years of duration.

TABLE IV : Distribution of cases of lisinopril group according to duration of diabetes mellitus.

Duration of DM (Years)	No.of cases	Percentage
1 - 5	8	47.1
6 - 10	5	29.4
11 - 15	1	5.9
16 - 20	3	17.6
TOTAL	17	100.0

Table IV shows the distribution of cases of lisinopril group according to their duration of diabetes mellitus. The maximum number (47.1%) of cases belonged to 1-5 years duration whereas minimum number (5.9%) were in the range of 11-15 years of duration of diabetes mellitus.

Table V shows the types of diabetes mellitus according to sex of the cases of captopril group. It is clear that 62.5% (about two third) patients belonged to NIDDM group whereas 37.5% patients belonged to IDDM group. In NIDDM group out of 10 cases, 7 were males and 3 females in IDDM group. The male : female ratio was 2 : 1.

TABLE V : Distribution of cases of captopril group according to their sex and type of diabetes mellitus.

Type of D.M.	Male		Female		Total	
	No.	%	No.	%	No.	%
NIDDM	7	63.6	3	60.0	10	62.5
IDDM	4	36.4	2	40.0	6	37.5
TOTAL	11	100.0	5	100.0	16	100.0

TABLE VI : Distribution of cases of lisinopril group according to their sex and type of diabetes mellitus.

Type of D.M.	Male		Female		Total	
	No.	%	No.	%	No.	%
NIDDM	5	50.0	4	57.1	9	52.9
IDDM	5	50.0	3	42.9	8	47.1
TOTAL	10	100.0	7	100.0	17	100.0

Table VI shows the type of diabetes mellitus and sex incidence. in lisinopril group of patients. There were 17 patients in this group. Out of which 10 were males and 7 females. Out of 10 male patients, 50% were NIDDM patients and rest 50% were IDDM, while 57.1% female patients were in NIDDM group and 42.9% in IDDM group. The maximum number of cases (52.9%) cases were in NIDDM group.

Table VII shows the effect of captopril on systolic and diastolic blood pressure in patients with

NIDDM after 2 months of therapy. The initial systolic blood pressure was 149.8±26.5 mm Hg which came down to 133.6±20 mm Hg after 2 months but the difference is statistically insignificant (p >0.05). Similarly the diastolic pressure fell from initial 82.4±13 mm Hg to 76.2±13 mm Hg after 2 months therapy, which is also insignificant (p >0.05).

TABLE VII : Showing the effect of captopril on blood pressure in NIDDM patients.

Sl. No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1.	170	100	142	90
2.	116	80	104	72
3.	160	74	150	70
4.	180	90	160	88
5.	140	80	120	60
6.	100	60	100	58
7.	150	92	140	86
8.	162	78	140	70
9.	140	70	130	72
10	180	100	150	96
Mean ±S.D.	149.8 ±26.5	82.4 ±13.0	133.6 ±20.0	76.2 ±13.0

p (0 - 2 months) >0.05

TABLE VIII : Showing the effect of lisinopril on blood pressure in NIDDM patients.

Sl. No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1.	160	110	140	90
2.	110	68	130	70
3.	140	100	142	86
4.	180	110	150	90
5.	140	80	120	70
6.	160	90	120	70
7.	150	90	120	86
8.	140	80	100	74
9.	130	82	120	70
Mean ±S.D.	145.6 ±20.1	90.0 ±14.4	126.9 ±15.2	78.4 ± 9.3

0 - 2 months : Systolic BP $p > 0.05$
Diastolic BP $p < 0.05$

Table VIII shows the effect of lisinopril on systolic and diastolic blood pressure in patients with NIDDM after 2 months of therapy. The initial systolic blood pressure was 145.6±20.1 mm Hg which came down to 126.9±15.2 mm Hg after 2 months but the difference was statistically insignificant($p > 0.05$) whereas the diastolic blood pressure fell from initial 90±14.4 mm Hg to 78.4 ±9.3 mm Hg after 2 months, which is statistically significant ($p < 0.05$).

TABLE IX : Statistical comparison of table VII and VIII.

Blood pressure	p values	
	0 month	2 months
Systolic	γ0.05	γ0.05
Diastolic	γ 0.05	γ0.05

Table IX shows the comparison of previous two tables at 0 and 2 months therapy. According to this table there was no difference between the effect of captopril and lisinopril in systolic and diastolic blood pressure at 0 and 2 months therapy.

TABLE X : Showing the effect of captopril in blood pressure of IDDM patients.

Sl. No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1.	140	80	120	70
2.	104	70	90	50
3.	100	60	96	60
4.	120	80	110	68
5.	120	90	100	78
6.	130	76	130	72
Mean ±S.D.	119.0 ±15.2	76.0 ±10.2	107.7 ±15.3	66.3 ± 9.9

(0 - 2 months) p γ0.05

Table X shows the effect of captopril on both type of blood pressure in patients with IDDM. At 0 month systolic blood pressure ranged from 100 to 140 mm Hg with a mean

value of 119±15.3 mm Hg. It came down to 107.7±15.3 mm Hg after 2 months therapy, but the difference is not significant ($p > 0.05$). Likewise the diastolic blood pressure which was ranging from 60 to 90 mm Hg with mean value of 76±10.2 mm Hg decreased to 66.3±9.9 mm Hg after 2 months therapy and the difference was not significant ($p > 0.05$).

TABLE XI : Effect of lisinopril on blood pressure in patients with IDDM.

Sl. No.	Blood pressure (mm Hg)			
	0 month		2 months	
	Systolic	Diastolic	Systolic	Diastolic
1.	150	100	130	90
2.	96	60	88	56
3.	110	70	98	56
4.	130	98	108	70
5.	130	80	108	80
6.	200	120	140	80
7.	140	80	130	60
8.	100	70	94	58
Mean ±S.D.	132.0 ±33.4	84.0 ±19.8	112.0 ±19.1	68.0 ±14.2

(0 - 2 months) Systolic BP $p > 0.05$
Diastolic BP $p < 0.05$

Table XI shows the effect of lisinopril on systolic and diastolic blood pressure in patients with IDDM. At 0 month systolic blood pressure ranged from 96 to 200 mm Hg with mean of 132±33.4 mm Hg. It came down to 112±19.1 mm Hg after 2 months of therapy, but

the difference was not significant ($p > 0.05$). The diastolic blood pressure which was ranging from 60 to 120 mm Hg (mean 84 ± 19.8) at the start of treatment decreased to 68 ± 14.2 mm Hg after 2 months therapy and the difference was statistically significant($p < 0.05$).

TABLE XII : Showing the statistical comparison of table X and XI.

Blood pressure	p values	
	0 month	2 months
Systolic	>0.05	>0.05
Diastolic	>0.05	>0.05

Table XII shows the comparison of the previous table X and XI at 0 and 2 months therapy. According to this table, both the values were statistically insignificant i.e. the systolic and diastolic blood pressures were similar at 0 and 2 months in captopril and lisinopril groups.

TABLE XIII : Showing the effect of captopril on 24 hours urinary protein excretion in NIDDM patients.

Sl. No.	Urine protein (mg/l)	
	0 month	2 months
1.	100	60
2.	120	80
3.	100	56
4.	350	250
5.	250	360
6.	35	25
7.	100	120
8.	125	100
9.	75	100
10.	140	130
Mean$\pm$S.D.	139.5 ± 92.4	128.1 ± 101.7

(0 - 2 months) $p > 0.05$

Table XIII shows the effect of captopril on 24 hour urinary protein excretion in patients of NIDDM. At the start of treatment the mean excretion was 139.5±92.4 mg/l which decreased to 128.1±101.7 mg/l after 2 months therapy of captopril. The difference was not significant statistically (p >0.05).

TABLE XIV : Showing the effect of lisinopril on 24 hours urinary protein excretion in patients of NIDDM.

Sl. No.	Urinary protein (mg/l)	
	0 month	2 months
1.	250	200
2.	200	300
3.	150	100
4.	180	200
5.	180	120
6.	150	138
7.	250	200
8.	200	174
9.	250	100
Mean±S.D.	201.1±40.7	158.0±82.0

(0 - 2 months) p >0.05

Table XIV shows the effect of lisinopril on 24 hours urinary protein excretion in patients of NIDDM. Initial mean urinary protein excretion was 201.1±40.7 mg/l. After 2 months therapy of lisinopril it was only 158±82 mg/l. The difference between 0 and 2 months values was not statistically significant (p >0.05).

Table XV shows the comparison of 0 and 2 months therapies of table XIII and XIV. At 0 months the 24 hours urinary protein excretion was higher in patients who were treated with lisinopril and the difference was statistically significant ($p < 0.05$), but after 2 months of therapy, both the values were not statistically significant ($p > 0.05$).

TABLE XV : Showing the comparison of table XIII and XIV statistically.

Treatment group (NIDDM)	Values of protein (Mean±SD)	
	0 month	2 months
Captopril	139.5±92.4	128.1±101.7
Lisinopril	201.1±40.7	158.0±82.0
p values	< 0.05	> 0.05

TABLE XVI : Effect of captopril on proteinuria in patients of IDDM.

Sl. No.	Urinary protein (mg/l)	
	0 months	2 months
1.	210	160
2.	300	260
3.	150	75
4.	100	50
5.	100	64
6.	150	90
Mean±S.D.	168.3±76.3	115.8±80.6

(0 - 2 months) $p > 0.05$

Table XVI shows the effect of captopril on proteinuria in IDDM patients. Initially 24 hour protein excretion was 168.3±76.3 mg/l which came down to 115.8± 80.6 mg/l but the difference was statistically insignificant ($p > 0.05$)

Table XVII shows the effect of lisinopril on proteinuria in IDDM patients. Initially 24 hour protein concentration was 138.8±88.7 mg/l while it was found to be 113.8±69.0 mg/l at 2 months, however the difference was not significant statistically ($p > 0.05$).

TABLE XVII : Effect of lisinopril on proteinuria in patients of IDDM.

Sl. No.	Urinary protein (mg/l)	
	0 month	2 months
1.	80	100
2.	80	72
3.	250	160
4.	130	140
5.	50	38
6.	120	100
7.	100	50
Mean ± S.D.	138.8±88.7	113.8±68.9

(0 - 2 months) $p > 0.05$

Table XVIII shows the comparison of mean of table XVI and XVII at 0 and 2 months. At both times there was no difference in the values of urinary protein excretion ($p > 0.05$).

TABLE XVIII : Showing the statistical comparison of thevalues of table XVI and XVII.

Treatment group (IDDM)	Urinary protein values (Mean±S.D.) 0 month	2 months
Captopril	168.3±76.3	115.8±80.6
Lisinopril	138.8±88.7	113.8±68.9
p value	>0.05	>0.05

TABLE XIX : Showing the effect of captopril on blood urea in patients of NIDDM.

Sl. No.	Blood urea (mg/dl) 0 month	2 month
1.	30	25
2.	38	30
3.	20	24
4.	63	60
5.	25	26
6.	24	28
7.	34	30
8.	28	25
9.	23	26
10.	50	35
Mean±S.D.	33.5±13.6	30.9±10.7

(0 - 2 months) $p > 0.05$

Table XIX shows the effect of captopril on blood urea in NIDDM patients. Initially the blood urea level was 33.5±13.6 mg/dl and apparently it fell to 30.9±10.9 mg/dl after 2 months treatment. But it was statistically insignificant ($p > 0.05$).

Table XX shows the effect of lisinopril on blood urea in NIDDM patients. At 0 month the values ranged from 20 to 34 mg/dl with mean values 26.4±5.5 mg/dl. It increased to 30.4±5.2 mg/dl. The difference was not statistically significant ($p > 0.05$).

TABLE XX : Showing the effect of lisinopril on blood urea in patients of NIDDM.

Sl. No.	Blood urea (mg/dl)	
	0 month	2 months
1.	34	38
2.	20	38
3.	20	24
4.	30	28
5.	24	30
6.	30	32
7.	20	28
8.	30	32
9.	30	24
Mean±S.D.	26.4±5.5	30.4±5.2

(0 - 2 months) $p > 0.05$

Table XXI shows the comparison of the table XIX and XX at 0 and 2 months and it was found that there was no statistical difference between the values at 0 and 2 months ($p > 0.05$).

TABLE XXI : Showing the statistical comparison of table XIX and XX.

Treatment group (NIDDM)	Mean blood urea (mg/dl)	
	0 month	2 months
Captopril	33.5±13.6	30.9±10.7
Lisinopril	26.4±5.5	30.4±5.2
p values	$p > 0.05$	$p > 0.05$

TABLE XXII : Showing the effect of captopril on blood urea in patients of IDDM.

Sl. No.	Blood urea (mg/dl)	
	0 month	2 months
1.	36	38
2.	34	28
3.	55	40
4.	28	24
5.	40	34
6.	33	30
Mean±S.D.	37.7±9.4	32.3±6.1

(0 - 2 months) $p > 0.05$

Table XXII shows the effect of captopril on blood urea in IDDM patients. It was 37.7±9.4 mg/dl at 0 months and it decreased to 32.3±6.1 mg/dl after 2 months of therapy but difference was not statistically significant ($p > 0.05$).

Table XXIII shows the effect of lisinopril on blood urea in patients of IDDM. At 0 months the values ranged from 17 to 46 mg/dl with a mean value 31.8±10.9 mg/dl. It slightly decreased to 31.4±7.9 mg/dl. The difference was statistically insignificant (p >0.05).

RABLE XXIII : Effect of lisinopril on blood urea in patients of IDDM.

Sl. No.	Blood urea (mg/dl) 0 months	2 months
1.	23	20
2.	42	40
3.	46	40
4.	17	33
5.	40	38
6.	30	32
7.	36	26
8.	20	22
Mean ± S.D.	31.8±10.9	31.4±7.9

(0 - 2 months) p >0.05.

TABLE XXIV : Showing the statistical comparison of table XXII and XXIII.

Treatment group IDDM	Blood urea (mean±SD, mg/dl 0 month	2 months
Captopril	37.7±9.4	32.3±6.1
Lisinopril	31.8±10.9	31.4±7.9
p values	>0.05	>0.05

Table XXIV shows the comparison of table XXII and XXIII. At 0 month the mean of caoptopril group did not differ from the mean values of lisinopril. Similarly the corresponding figures at 2 months also did not differ statistically ($p > 0.05$).

Table XXV shows the effect of captopril on serum creatinine in NIDDM group. Initially it was 1.1 ± 0.2 mg/dl and it came down to 1.0 ± 0.2 mg/dl after 2 months of therapy. The difference was not significant statistically ($p > 0.05$).

TABLE XXV : Effect of captopril on serum creatinine in patients of NIDDM.

Sl. No.	Serum creatinine (mg/dl). 0 months	2 months
1.	1.0	0.9
2.	1.0	0.8
3.	1.3	1.2
4.	1.0	1.2
5.	0.9	0.8
6.	1.0	1.0
7.	1.2	1.3
8.	1.3	1.0
9.	1.3	1.2
10.	1.0	0.8
Mean $\pm$ S.D.	1.1 ± 0.2	1.0 ± 0.2

Table XXVI shows the effect of lisinopril on serum creatinine in patients with NIDDM. The mean values of serum creatinine at 0 months was 1.0±0.4 mg/dl and it remained constant at 1.0±0.3 mg/dl after 2 months of treatment with lisinopril.

TABLE XXVI : Effect of lisinopril on serum creatinine in patients with NIDDM.

Sl. No.	Serum creatinine (mg/dl)	
	0 month	2 months
1.	1.2	1.2
2.	1.5	1.4
3.	1.3	1.0
4.	0.9	1.0
5.	0.9	1.0
6.	0.6	0.4
7.	0.7	0.8
8.	1.5	1.3
9.	0.7	0.8
Mean ± S.D.	1.0±0.4	1.0±0.3

Table XXV and XXVI have been compared in table XXVII. At 0 month though there was apparent slight difference but it was statistically significant ($p < 0.05$). The values after 2 months therapy were also same in both the groups.

TABLE XXVII : Comparison between table XXV and XXVI.

Treatment group (NIDDM)	Serum creatinine (mean±S.D., mg/dl) 0 month	2 months
Captopril	1.1±0.2	1.0±0.2
Lisinopril	1.0±0.4	1.0±0.3
p values	>0.05	No difference

TABLE XXVIII : Effect of captopril on serum creatinine in patients of IDDM.

Sl. No.	Serum creatinine (mg/dl) 0 month	2 months
1.	1.6	1.4
2.	1.3	1.2
3.	1.8	1.4
4.	0.8	0.7
5.	2.3	1.7
6.	0.8	0.9
Mean±S.D.	1.4±0.6	1.2±0.4

(0 - 2 months) p >0.05

Table XXVIII shows the effect of captopril on serum creatinine in IDDM cases. The mean values of 1.4±0.6 mg/dl fell down to 1.2±0.4 mg/dl after 2 months therapy of captopril. But the difference was not statistically significant (p >0.05).

Table XXIX shows the effect of lisinopril on serum creatinine in IDDM cases after 2 months of treatment Initially the mean values were 1.3±0.4 mg/dl and it fell down to 1.2±0.3 after 2 months therapy. The difference was insignificant statistically (p >0.05).

TABLE XXIX : Effect of lisinopril on serum creatinine in IDDM patients.

Sl. No.	Serum creatinine (mg/dl)	
	0 month	2 months
1.	1.3	1.2
2.	1.6	1.5
3.	1.8	1.8
4.	0.6	0.8
5.	1.4	1.2
6.	1.5	1.3
7.	1.2	1.0
8.	1.0	0.9
Mean±S.D.	1.3±0.4	1.2±0.3

(0 - 2 months) p >0.05

Table XXX compares the values of table XXVIII and XXIX. There was no difference statistically between the values of two groups either 0 or 2 months(p >0.05).

TABLE XXX : Showing the statistical comparison between table XXVIII and XXIX.

	0 month	2 months
p value	>0.05	>0.05

Table XXXI shows the effect of captopril on GFR in NIDDM patients. Initially the mean values of GFR was 68.9±13.2 ml/min and this value increased to 73.0±14.5 ml/min after 2 months, but the difference was statistically insignificant (p >0.05).

TABLE XXXI : Effect of captopril on GFR in patients of NIDDM.

Sl.	Glomerular filtration rate(ml/min)	
	0 MONTH	2 months
1.	63.0	70.0
2.	69.5	86.9
3.	53.8	58.3
4.	83.1	69.3
5.	94.4	106.3
6.	67.1	67.1
7.	71.6	66.1
8.	58.3	75.8
9.	52.1	56.5
10.	76.5	73.5
Mean±S.D.	68.9±13.2	73.0±14.5

(0 -2 months) p >0.05

Table XXXII shows the effect of lisinopril on GFR in NIDDM patients. It was 69.1±25.6 ml/min at 0 month and it increased to 70.3±21.2 ml/min after 2 months but the difference was statistically insignificant (p >0.05).

TABLE XXXII : Effect of lisinopril on GFR in patients of NIDDM.

Sl. No.	Gloermular filtration rate (ml/min)	
	0 month	2 months
1.	58.3	58.3
2.	37.8	47.8
3.	51.6	68.5
4.	71.8	64.6
5.	74.1	66.7
6.	87.3	104.7
7.	80.2	70.2
8.	41.0	47.3
9.	119.9	104.9
Mean±S.D.	69.1±25.6	70.3±21.2

(0 - 2 months) p >0.05

Table XXXIII shows the comparison of table XXXI and XXXII. At 0 months as well as 2 months, the values of two tables do not statistically differ (p >0.05).

TABLE XXXIII : Comparison of table XXXI and XXXII.

	0 month	2 months
p value	>0.05	>0.05

TABLE XXXIV : Effect of captopril on GFR in patients of IDDM.

Sl. No.	Glomerular filtration rate (ml/min) 0 month	2 months
1.	60.0	70.0
2.	57.0	62.3
3.	43.3	56.1
4.	108.9	124.4
5.	41.7	56.5
6.	82.6	73.4
Mean$\pm$SD	65.6$\pm$25.8	72.8$\pm$26.7

(0 - 2 months) $p > 0.05$

Table XXXIVshows the effect of captopril on GFR in IDDM patients. Initially the mean values was 65.6$\pm$25.8 ml/min. It increased to 72.8$\pm$26.7 ml/min after 2 months. But the difference was not significant statistically ($p > 0.05$).

Table XXXV shows the effect of lisinopril on GFR in patients of IDDM. The mean GFR was 72.1$\pm$33.0 ml/min at 0 month. It decreased to 70.6$\pm$24.2 ml/min after 2 months. The difference was statistically insignificant ($p > 0.05$).

TABLE XXXV : Effect of lisinopril on GFR in patients of IDDM.

Sl. No.	Glomerular filtration rate (ml/min)	
	0 month	2 months
1.	56.5	61.3
2.	53.1	56.7
3.	50.9	50.9
4.	118.8	89.4
5.	54.5	63.5
6.	33.6	38.8
7.	119.9	104.9
8.	89.4	99.3
Mean±S.D.	72.1±33.0	70.6±24.2

(0-2 months) $p > 0.05$

TABLE XXXVI : Comparison between table XXXIV and XXXV.

	0 month	2 months
p value	> 0.05	> 0.05

Table XXXVI shows the comparison of table XXXIV and XXXV. At 0 month and 2 months both the values were not statistically significant ($p > 0.05$).

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D I S C U S S I O N

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D I S C U S S I O N

Present study was carried out in 33 patients of diabetic nephropathy, who were attending diabetic clinic regularly at M.L.B. Medical College, Jhansi. Out of 33, 16 patients were included in captopril group and remaining 17 in lisinopril group.

Captopril Group

Sixteen patients were included in captopril group, 11 were males and 5 females. Maximum number of cases belonged to age group 41-50 years (37.5%). Out of 16 patients, 10(62.5%) were having non-insuline dependent Diabetes Mellitus and rest had Insulin dependent Diabetes Mellitus.

Lisinopril Group

Seventeen cases were included in lisinopril group, out of which, 10 were males and 7 females. Maximum number of cases were in age group of 51-60 years (29.5%). Out of 17 patients, 9(52.9%) were having noninsulin dependent Diabetes Mellitus, while 8(47.1%) had Insulin dependent Diabetes Mellitus.

Maximum duration of Diabetes Mellitus in captopril group was 1-5 years in 9(56.3%) patients, while in lisinopril group, the duration was same in 8(47.1%) patients. All of these patients were having significant proteinuria despite short duration of diabetes mellitus.

Bjorck Staffan et al (1986) studied 15 patients with insulin dependent diabetess. All patients had diabetic nephropathy and mean duration of diabetes was 22 years. All of them were given captopril and frusemide in combination.

In present study, such short duration of diabetes mellitus could be because of late diagnosis. In Bundelkhand region most of the patients are illiterate and socio-economically poor and they are not aware of the symptoms of Diabetes Mellitus.

EFFECT ON BLOOD PRESSURE

Captopril Group

In NIDDM, mean systolic blood pressure at 0 month was 149.8±26.5 mm Hg which came down to 133.6±20. mm Hg after two months. This change is insignificant ($p > 0.05$). Similarly the diastolic blood pressure fell from initial 82.4±13.0 mm Hg to 76.2±13.0 mm Hg after 2 months, again this decrease is insignificant($p > 0.05$). It is due to the fact that in present study most of the cases were normotensive while only 2 patients were having mild hypertension.

Similarly it was not observe any significant decrease in systolic and diastolic blood pressure in IDDM patients, who were given captopril. Again it is because there was no hypertensive patient in this group and the dose of captopril used was too low to cause hypotension.

Lisinopril Group

In NIDDM patients the mean systolic blood pressure fell from 145.6±20.1 mm Hg to 126.9±15.2 mm Hg. This change is insignificant ($p > 0.05$) while mean diastolic blood pressure fell from initial 90±14.4 to 78.4±9.3 mm Hg after 2 months but this decrease is significant ($p < 0.05$). It may be due to the fact that 33% patients in this group were having mild to moderate hypertension.

Similarly in IDDM patients, the mean systolic blood pressure fell from 132.0±33.4 to 112.0±19.1 mm Hg and this change is insignificant ($p > 0.05$) while mean diastolic blood pressure fell from 84.0±19.8 to 68±14.2 mm Hg, but this change is significant ($p < 0.05$). In this group also, 2 patients had mild hypertension and another patient had severe hypertension.

EFFECT OF PROTEINURIA

In present study, 16 patients were included in captopril group. Out of 16 patients, 10 were related to NIDDM. In these patients initially mean urinary protein excretion was 139±92.4 mg/l which fell down to 128±101.7 mg/l. This difference is statistically insignificant ($p > 0.05$).

In lisinopril group, 17 patients were included. Out of which, 9 patients were related to NIDDM. In

these patients, initially mean urinary protein was 201.1±40.7 mg/l. After 2 months therapy the mean excretion was only 158±82 mg/l. The fiference is insignificant (p 70.05).

These drugs were also given to patients related to IDDM group in which 6 patients were treated with captopril while 8 patients with lisinopril. Similarly in these both groups, protein excretion was reduced but difference is statistically insignificant (p 70.05).

On comparing the captopril group to lisinopril group according to their efficacy in reducing proteinuria, the difference is insignificant (p 70.05). With present study it can be said that there is no difference between captopril and lisinopril regarding effect on proteinuria in diabetic nephropathy.

According to Bjorck Staffan et al (1986), 14 patients of diabetic nephropathy were treated with captopril for 2 years. The mean urinary protein excretion was 2.9(2.0) gm/24 hours before and 2.8(1.9) gm/24 hours after treatment. Protein excretion was reduced in 10 of the 14 patients but this decreased protein excretion was statistically insignificant.

According to Yoshio Taguma et al (1985) 10 azotemic diabetic with heavy proteinuria were treated with captopril (37.5 mg/day) for 2 months. Urinary protein decreased promptly within two weeks from 10.6±2.2 to

6.1±1.4 gm/day. This decrease of protein excretion was statistically significant($p < 0.01$).

In present study, the effect of captopril and lisinopril on mean urinary protein excretion was not significant but proteinuria was reduced in most of the patients. But Taguma et al reported that treatment with captopril reduced proteinuria in diabetic nephropathy. The patients in their study, however, different from present study,. They were much older and had more severe proteinuria, congestive heart failure was common among their patients but was present in none of our patients. Differences between the patients may therefore explain the different effects of captorpil on proteinuria.

EFFECT ON RENAL FUNCTION

Blood Urea :

In present study 10 patients of NIDDM were treated with captopril and 9 patients with lisinopril. In captopril group, initially the mean blood urea was 33.5±13.6 mg/dl which fell down to 30.9±10.7 mg/dl after 2 months' treatment. This difference is statistically insignificant ($p > 0.05$), but in patients with lisinopril group the mean value of blood urea was increased from 26.4±5.5 to 30.4±5.2 mg/dl and again this difference is insignificant ($p > 0.05$).

Similarly 6 patients of IDDM were treated with captopril and 8 patients with lisinopril (Table XXII &

XXIII) but difference of values of both groups after 2 months treatment were statistically insignificant ($p > 0.05$).

On comparing the results of captopril and lisinopril as mentioned above, in NIDDM patients, the levels of blood urea slightly increased in lisinopril group while in case of captopril the level of blood urea decreased but in IDDM patients the values of blood urea decreased in both groups.

Statistical comparison of both drugs shows that effects of captopril and lisinopril are the same ($p > 0.05$) on blood urea. The insignificant effect on blood urea could be because most of the values were within normal range (Table XIX, XX, XXII and XIII).

SERUM CREATININE

Same patients were also investigated for serum creatinine before and after 2 months of therapy. In NIDDM patients of captopril group, the mean serum creatinine decreased from 1.1 ± 0.2 to 1.0 ± 0.2 mg/dl but in NIDDM patients of lisinopril group the values were same before and after 2 months of therapy. The changes were not statistically significant ($p > 0.05$).

Similarly IDDM patients of captopril group were also investigated and serum creatinine decreased from 1.4 ± 0.6 to 1.2 ± 0.4 mg/dl but in IDDM patients of lisinopril group, the mean values decreased from 1.3 ± 0.4 to 1.2 ± 0.3 mg/dl. Again these changes are statistically

insignificant ($p > 0.05$). Statistical insignificant effect on serum creatinine is because all initial findings of serum creatinine were within normal limits.

According to Bjorck Staffan et al (1986) 13 patients were treated with captopril and frusemide in combination for 2 years. All patients had diabetic nephropathy. The mean serum creatinine concentration was 2.1 mg/dl before treatment and 2.5 mg/dl at the end of the follow up period.

According to Siphae Lee et al (1990) 11 patients of diabetic nephropathy were treated with captopril for 24 months and serum creatinine increased from 1.72 ± 0.43 mg/dl($N = 11$) to 3.45 ± 0.67 mg/dl($N = 6$), this increase was statistically significant ($p < 0.01$).

GLOMERULAR FILTRATION RATE

In present study, GFR was calculated in 10 patients of NIDDM who were treated with captopril while 9 patients of NIDDM were treated with lisinopril. In captopril group, initially the mean GFR was 68.9 ± 13.2 ml/min and it increased to 73.0 ± 14.5 it increased to 73.0 ± 14.5 ml/min after 2 months of therapy. This difference is insignificant ($p > 0.05$), and in patients of lisinopril group the GFR increased from 69 ± 25.6 to 70.3 ± 21.2 ml/min which is again insignificant($p > 0.05$).

Similarly 6 patients of IDDM were treated with captopril and 8 patients with lisinopril and results are shown in table XXXIV and XXXV but difference of values of both groups after 2 months were statistically insignificant ($p > 0.05$).

On comparing, results show that effect of captopril and lisinopril on renal function are almost same, and it was maintained through out the study period.

According to Mogensen et al (1982), Poring et al (1983), Bjorck Staffan et al (1986), Eva Hommel (1986), Parving (1988) and Siphae Lee et al (1990) the effect of angiotensin converting enzyme inhibitors on renal function was almost same and maintained through out the study period. ACE inhibitors delayed the renal failure which is much similar to present study.

C O N C L U S I O N

C O N C L U S I O N

In this study, 16 patients in captopril group and 17 in lisinopril group were studied to find out the effect on proteinuria and renal function in hypertensive and non hypertensive patients of diabetic nephropathy. In this study the comparative effect of both drugs was also analysed.

The following conclusions were drawn from the present study.

1. The effect of lisinopril is better than captopril in hypertensive patients. The fall in diastolic blood pressure was statistically significant ($p < 0.05$) in patients of lisinopril group as compared to captopril group ($p > 0.05$).
2. The proteinuria in both groups after 2 months of treatment decreased but it was statistically insignificant ($p > 0.05$).
3. No difference was observed in both groups of patients (Captopril versus lisinopril) in relation to antiproteinuric effects.
4. Statistical insignificant changes were observed on blood urea, serum creatinine and GFR in both groups.
5. Overall results show that there is not much difference between captopril and lisinopril regarding the effect on proteinuria and renal function in diabetic nephropathy.

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B I B L I O G R A P H Y

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B I B L I O G R A P H Y

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